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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,481	GRAAF ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed March 15, 2004 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Applicants canceled all pending claims (e.g., 1-31) and added claims 32-51. Therefore, claims 32-51 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The Tuschl rejections under 35 U.S.C. § 102(b) and 35 U.S.C. 103(a) are withdrawn in view of Applicants' amendments and/or arguments. All other rejections are maintained and the arguments are addressed below.

Outstanding Rejections

Claim Rejections - 35 USC § 112

5. Claims 32-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination

of Patent Applications Under the 35 USC 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

With respect to adequate disclosure Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples*, which provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention.* See *In re Riat*_(CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure).

In this case, the number of claimed nucleic acid sequences is very large. Applicants claim recombinant vectors of any origin (e.g., viral, plasmid, etc.) that can infect host cells of any type (e.g., human, bacterial, yeast, etc.) via any mechanism (e.g., replicate, integrate, etc.) using any snRNA (U1, U2, U3 ... etc.) with any restriction enzyme (e.g., StyI, BaeI, XhoI). However, Applicants provide only ONE example in the specification drawn to a pSP-luc+ plasmid using 293T cells and a U1 snRNA with the BaeI enzyme (e.g., see specification, pages 21-23). Consequently, it is the Examiner's position that one example is not representative of the infinite number of vectors that are currently claimed because the claims encompass a wide variety of different species (e.g., different origin, mechanism, host cell type). When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the

variation within the genus (e.g., see MPEP § 2163.05). In addition, the more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure.

The CAFC has also stated that a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)] (the case is referred to herein as "*Lilly*"). Here, the instant claims define the components of the recombinant vector only by their functional properties (e.g., ability to splice). The CAFC held this sort of functional definition insufficient to adequately describe the claimed product.

Response

6. Applicant's arguments directed to the above written description rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue that the inventive portion of the subject matter was disclosed and that any additional variability within the genus arises due to additional elements that are not part of the inventor's contribution. Applicants point to the disclosure of "a vector containing a

nucleotide sequence encoding an snRNA, which sequence has been modified to allow for excision of a restriction fragment and insertion of a nucleotide sequence complementary to a predetermined sequence" in support of this position. Applicants further argue that any additional elements are well within the level of skill in the art including the selection of appropriate vectors and restriction enzymes (e.g., see 10/29/2003 Response).

This is not found persuasive for the following reasons:

The Examiner contends that the terms discussed in the rejection (i.e., "the inventive portion of the subject matter") are *relative*, *broad* and *open-ended* (e.g. see above rejection, "Applicants claim recombinant vectors of ***any*** origin (e.g., viral, plasmid, etc.) that can infect host cells of ***any*** type (e.g., human, bacterial, yeast, etc.) via ***any*** mechanism (e.g., replicate, integrate, etc.) using ***any*** snRNA (U1, U2, U3 ... etc.) with ***any*** restriction enzyme"), which encompass an infinite number of variations. The scope of these claims include an infinite number of sequences because the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form said sequences (i.e., no structural limitations have been set forth).

The CCPA stated, "The essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." *In re Barker*, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978). Another objective is to put the public in possession of what the applicant claims as the invention so that the public may ascertain if the patent applicant claims anything that is in common use, or already known. *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356 (1822). Furthermore, the language of the specification should describe the claimed invention so

that one skilled in the art can recognize what is claimed. A description of a compound in terms of its function fails to distinguish the compound from others having the same activity or function. A description of what a material does, rather than of what it is, ***usually does not suffice***. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175).

Here, the Examiner contends that the specification provides only **ONE** example of a vector (e.g., a pSP-luc+ plasmid using 293T cells and a U1 snRNA with the BaeI enzyme), which does not adequately describe the infinite number of variations currently claimed. The scope of these claims include an infinite number of sequences because the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form said sequences (i.e., no structural features are set forth). Applicants' arguments do not overcome this rejection because when (as is the case here) there is little to no disclosure in the instant specification of the starting material or conditions under which claimed process can be carried out, this failure cannot be rectified by asserting that all disclosure related to the process is within skill of art. *Genentech Inc. v. Novo Nordisk A/S* (CA FC) 42 USPQ2d 1001 (3/13/1997).

Also, the rejection notes that there is a greater need for representative examples in an unpredictable art. See *In re Riat* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr* (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and *University of California v. Eli Lilly and Co* cited above (for disclosure). For example, the Board has held that "the unpredictability

of an art area alone may be enough to create a reasonable doubt as to the accuracy of statements in the specification." Ex parte Singh, 17 U.S.P.Q.2d 1714,1716 (B.P.A.I. 1990). Thus, when claims encompass a broad genus (as is the case here) with widely varying structures that would not be expected to function in a similar manner due to their diverse nature (e.g., the vectors are of ***any*** origin (e.g., viral, plasmid, etc.) that can infect host cells of ***any*** type (e.g., human, bacterial, yeast, etc.) via ***any*** mechanism (e.g., replicate, integrate, etc.)) then a greater showing in the specification must be set forth. This has not been done. Consequently, the Examiner contends that Applicants' claimed scope represents only an invitation to experiment.

Accordingly, the written description rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 32-34, 36, 41-42, 44-48 and 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**).

For ***claims 32 and 42***, Noonberg et al. (see entire document) disclose antisense, triplex, and/or ribozyme oligonucleotide constructs i.e., vectors (see Noonberg et al., abstract), which anticipates claims 32 and 42. For example, Noonberg et al. disclose a

recombinant vector comprising an isolated nucleotide sequence encoding a snRNA, wherein said nucleotide sequence has been modified to contain one or more restriction sites, such that digestion with at least one restriction enzyme excises a restriction fragment and forms insertion sites in said nucleotide sequence (e.g., see figures 4B and 9 wherein a U6 snRNA vector is shown that has XhoI and NsiI restriction sites for inserting synthetic sequences; see also page 25, paragraph 2; see also page 36, paragraph 2; see also page 41, last paragraph; see especially page 50, Example 3, "The human U6 gene [snRNA] cloned within the SmaI site of pGem1 [recombinant vector] (Promeg, Madison, WI), along with a mutant human U6 gene with bases +25 to +55 replaced by an XhoI restriction site ... were ... provided"; see also page 56, paragraph 2; see also claim 24; see also page 9, lines 9-10). Finally, Noonberg et al. also disclose insertion an insertion cassette against a predetermined target (e.g., see page 35, paragraph 1, "The oligonucleotides can be designed for binding to different regions of different DNA or RNA targets, to different regions of the same DNA or RNA target, or to the same region of the same DNA or RNA target. Decisions as to vector design would be based upon whether the experimenter wanted to hit multiple targets broadly or a single target intensely"; see also figure 2(a) wherein the insertion of multiple oligos [i.e., a cassette] are shown; see also page 6, line 10; see also page 8, line 1; see also page 10, line 18; see also page 15, first full paragraph; see also page 38, line 31; see also page 39, lines 8-13; see also page 40, last paragraph; see also page 43, last paragraph; see also page 49, Example 2; see also page 2, Antisense section).

For ***claims 33-34 and 44-45***, Noonberg et al. disclose, for example, U6 snRNAs (e.g., see figure 4; see also page 50, Example 3; see also page 38, line 10; see also figures 19-21; see also pages 22-23; see also page 87, paragraph 2-3; see also page 93, last paragraph).

For ***claims 36 and 47-48***, Noonberg et al. disclose any restriction site including XhoI, NsiI wherein the restriction sites are excised to produce a double stranded insert (e.g., see page 33, paragraph 2, "Of course the XhoI and NsiI restriction sites can be replaced with ***any*** first and second unique restriction enzyme sites to facilitate insertion of the specific nucleotide sequence").

For ***claim 41 and 51***, Noonberg et al. disclose overhanging ends that are complementary (e.g., see page 51, line 7).

For ***claim 46***, Noonberg et al. disclose 30 bp insert (e.g., see page 50, Example 3 wherein insert is U6 gene from +25 to +55, which is 30 bp long).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 32-36, 41-48 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**) and the admission of prior art in the Specification and Cohen et al. (Cohen, J. B.; Snow, J. E.; Spencer, S. D.; Levinson, A. D. "Suppression of mammalian 5' splice-site defects by U1 small nuclear RNAs from a distance" PNAS 1994, 91, 10470-10474) (see IDS 3, reference AT) and Tuschl et al. (Tuschl, T.; Sharp, P. A.; Bartel, D. P. "Selection in vitro of novel ribozymes from a partially randomized U2 and U6 snRNA library" EMBO **1998**, 17, 9, 2637-2650).

For ***claims 32-34, 36, 41-42, 44-48 and 51***, Noonberg et al. teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 32-34, 36, 41-42, 44-48, 51 and, consequently, also renders obvious claims 32-34, 35, 41-42, 44-48 and 51.

The prior art teachings of Noonberg et al. differ from the claimed invention as follows:

For ***claims 35 and 43***, Noonberg et al. is deficient in that it does not specifically teach the use of U1 snRNA recombinant vector or U1 snRNA recombinant vector with

insertion cassette wherein the sequence has been modified within the first 11 nucleotides of the coding region.

However, the admission in the specification and the Cohen et al. and Tuschl et al. references teaches the following limitations that are deficient in Noonberg et al.:

For ***claims 35 and 43***, Tuschl et al. (see entire document) discloses a recombinant vector encoding U2 and U6 snRNA with a 40 nucleotide insertion cassette contained between two insertions sites (see Tuschl et al., figures 1-2, see also Materials and Methods, Pool Construction, selection and amplification). Furthermore, the admission in the specification combined with the reference that the specification refers to (i.e., the Noonberg et al. reference) teach that a person of skill in the art would recognize the value of using any U snRNA including U1 snRNA extending the teaching of Tuschl et al. from U2/U6 to U1 snRNA (e.g., see specification, Background of the Invention, page 1, last paragraph, "There has long been interest in utilizing the various splicing functions of individual U snRNA to inhibit or modify transcription, and, thereby, to suppress undesired expression products (Cohen, J. B., et al., 1994, PNAS 91:10470-10474) [which specifically cites the use of U1 snRNA, see entire document, especially abstract and Materials and Methods section]). Such suppression has enormous therapeutic potential"). Furthermore, Cohen et al. teach a modification within the first 11 nucleotides (e.g., see Figure 3 A, U1-αA5 which has a mutation in the "fifth" position which is within the first eleven nucleotides).

It would have been obvious to one skilled in the art at the time the invention was make a recombinant vector encoding snRNA with an insertion cassette as taught by

Noonberg et al. with the U1 snRNA cassette vector as taught by the admission in the specification and the Cohen et al. and Tuschl et al. references because the admission in the specification teaches that any U snRNA would be a candidate for recombinant technology and specifically points to U1 snRNA by citing the Cohen et al. reference (see specification, page 1, last paragraph; see also Cohen et al. reference, entire document). Furthermore, one of ordinary skill in the art would have been motivated to use the U1 snRNA as taught by the admission in the specification and Cohen et al. because according to the specification modification of such a snRNA would have "enormous therapeutic potential" and specifically recites a reference (i.e., the Cohen et al. reference) that addresses the use of U1 snRNA. In addition, Noonberg et al. teach that their invention is "an improved method" for the delivery of ribozymes (e.g., see Noonberg et al., page 1, line 24; see also page 14, line 27; see especially page 24, last paragraph), which would encompass the ribozymes disclosed by Cohen et al. and Tuschl et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all the references teach that recombinant U snRNAs can be made into a vector and mutated. In addition, Noonberg et al. states that "***any*** oligonucleotide that is desired to be transcribed within the cell [can be used] ... including ... a ribozyme" (e.g., see paragraph bridging pages 29-30), which specifically points toward the ribozyme papers of Cohen et al. and Tuschl et al. Furthermore, Noonberg et al. states that the advantages of using their invention with ribozymes like those disclosed by Cohen et al. and Tuschl et al. are that "RNA polymerase III transcribes at a nearly constant rate and

high frequency in almost all mammalian cell types ... [and] are also highly efficient allowing for clean transcription" (e.g., see Cohen et al., page 36, first full paragraph).

11. Claims 32-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noonberg et al. (WO 95/10607) (Date of Patent is **April 20, 1995**) and the admission of prior art in the Specification and Cohen et al. (Cohen, J. B.; Snow, J. E.; Spencer, S. D.; Levinson, A. D. "Suppression of mammalian 5' splice-site defects by U1 small nuclear RNAs from a distance" PNAS 1994, 91, 10470-10474) (see IDS 3, reference AT) and Tuschl et al. (Tuschl, T.; Sharp, P. A.; Bartel, D. P. "Selection in vitro of novel ribozymes from a partially randomized U2 and U6 snRNA library" *EMBO* **1998**, *17(9)*, 2637-2650) (of record) and Sears et al. (Sears, L. E.; Zhou, b.; Aliotta, J. M.; Morgan, R. D.; Kong, H. "BaeI, another unusual BcgI-like restriction endonuclease" *Nucleic Acids Research* **1996**, 24(18), 3590-3592).

For ***claims 32-36, 41-48 and 51***, the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification teaches all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 32-36, 41-48 and 51.

The prior art teaching of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification differ from the claimed invention as follows:

For ***claims 37-40 and 49-50***, the prior art teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification differ from the claimed invention by not specifically reciting the use of a BaeI or the complements of DNA sequences of SEQ ID NO: 2 and SEQ ID NO: 3. The prior art teachings of Noonberg et

al., Cohen et al., Tuschl et al. and Applicants' admission in the specification only state that "any first and second unique restriction enzyme sites to facilitate insertion of the specific nucleotide sequence" can be used and provide XhoI and NsiI as examples, but do not explicitly refer to BaeI (e.g., see Noonberg et al., page 33, paragraph 1).

However, Sears et al. teach the following limitations that are deficient in the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification:

For ***claims 37-40 and 49-50***, Sears et al. (see entire document) teach the use of BaeI on double stranded DNA (e.g., see Sears et al., figure 2-4). In addition, the Examiner argues that the insertion sites produced by BaeI would "inherently" produce SEQ ID NO:2 and SEQ ID NO:3 because Applicants explicitly state, "its [i.e., BaeI] cleavage sites are 5'-GCAGG-3' (SEQ ID NO: 2) and 5'-TGAGA-3' (SEQ ID NO:3)" (see specification, page 18, first full paragraph). Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP § 2112.01.

It would have been obvious to one skilled in the art at the time the invention was made to make the recombinant snRNA vectors as taught by the combined teachings of

Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification with the BaeI restriction enzyme as taught by Sears et al. because Noonberg et al. explicitly states that any restriction enzyme can be used (e.g., see Noonberg et al., page 33, paragraph 1), which would encompass BaeI. Furthermore, one of ordinary skill in the art would have been motivated to use BaeI and would have reasonably expected to be successful because Sears et al. teach that BaeI can be used advantageously with double-stranded DNA (e.g., see Sears et al., abstract), which would include the dsDNA vectors disclosed by the combined teachings of Noonberg et al., Cohen et al., Tuschl et al. and Applicants' admission in the specification.

Response

12. Applicant's arguments directed to the Tuschl et al. 35 U.S.C. § 103(a) rejection (e.g., see 10/29/2003 Response, pages 9-10) were fully considered (and are incorporated in their entirety herein by reference) as they apply to the new 35 U.S.C. §103(a) rejection cited above but were not deemed persuasive.

[1] Applicants argue that the specification cannot be relied upon for motivation and cite MPEP § 706.02(j) in support of this position (e.g., see 10/29/2003 Response, pages 9-10).

[2] Tuschl et al. does not teach the elements of "single snRNA" of claim 32 and an insertion cassette that is directed against a "predetermined target" of claim 42 (e.g., see 10/29/2003 Response, first full paragraph and third full paragraph).

[3] Tuschl et al. expressly teach away from using a single snRNA by teaching that snRNAs are not known to be catalytic in the absence of other spliceosomal components (e.g., see 10/29/2003 Response, page 10, second full paragraph).

[4] There is no motivation to combine (e.g., see 10/29/2003 Response, page 10, second full paragraph).

This is not found persuasive for the following reasons:

[1] The Examiner contends that Applicants' admission in the specification is being relied upon in accordance with MPEP § 2129 (e.g., see MPEP § 2129, "When applicant states that something is prior art, it is taken as being available as prior art against the claims. *Admitted prior art can be used in obviousness rejections*." *In re Nomiya*, 509 F.2d 566, 184 USPQ 607, 611 (CCPA 1975) (Figures in the application labeled "prior art" held to be an admission that what was pictured was prior art relative to applicant's invention)).

[2] In response to applicant's arguments against the Tuschl reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the "single snRNA" and the "predetermined targets" are taught by the "combined" references as outlined above.

[3] Tuschl et al. do not teach away because the reference provides specific examples of U2 and U6 snRNA (e.g., see abstract, "Combinatorial libraries related to spliceosomal U2 and U6 snRNAs were tested for catalytic reactions typical of the splicing of nuclear pre-mRNAs"). Furthermore, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See MPEP § 2123.

[4] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some

teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation is as follows (see also rejection above):

> Furthermore, one of ordinary skill in the art ***would have been motivated*** to use the U1 snRNA as taught by the admission in the specification and Cohen et al. because according to the specification modification of such a snRNA would have "enormous therapeutic potential" and specifically recites a reference (i.e., the Cohen et al. reference) that addresses the use of U1 snRNA. In addition, Noonberg et al. teach that their invention is "an improved method" for the delivery of ribozymes (e.g., see Noonberg et al., page 1, line 24; see also page 14, line 27; see especially page 24, last paragraph), which would encompass the ribozymes disclosed by Cohen et al. and Tuschl et al. Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because all the references teach that recombinant U snRNAs can be made into a vector and mutated. In addition, Noonberg et al. states that "***any*** oligonucleotide that is desired to be transcribed within the cell [can be used] ... including ... a ribozyme" (e.g., see paragraph bridging pages 29-30), which specifically points toward the ribozyme papers of Cohen et al. and Tuschl et al. Furthermore, Noonberg et al. states that the advantages of using their invention with ribozymes like those disclosed by Cohen et al. and Tuschl et al. are that "RNA polymerase III transcribes at a nearly constant rate and high frequency in almost all mammalian cell types ... [and] are also highly efficient allowing for clean transcription" (e.g., see Cohen et al., page 36, first full paragraph).

Accordingly, Applicants' arguments with regard to the previous Tuschl et al. 35 U.S.C. § 103(a) rejection (see 10/29/2003 Response, pages 9-10) do not necessitate the withdrawal of the new 35 U.S.C. § 103(a) rejections cited above.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 24, 2004

BENNETT CELSA
PRIMARY EXAMINER